

IT IS CLAIMED:

1. An antisense compound having an uncharged morpholino backbone and a base sequence between 12 and 25 nucleotide bases in length which is complementary to a target region of a selected preprocessed mRNA coding for a protein selected from the group consisting of *myc*, *myb*, *rel*, *fos*, *jun*, *abl*, *bcl*, *p53*, an integrin, a cathedrin, a telomerase, a cytokine, a kinase, a receptor protein, hCG, HIV rev, human papilloma virus, and human parvovirus B19,

where the 5' end of the target region is 1-25 bases downstream of a normal splice acceptor site in said preprocessed mRNA.

2. The compound of claim 1, having intersubunit linkages selected from the group consisting of the structures presented in Figs. 2AA-2EE.

3. The compound of claim 2, wherein the linkage is a phosphorodiamidate linkage as represented at Figure 2B-B, where  $X=NH_2$ ,  $NHR$ , or  $NRR'$ ,  $Y=O$ , and  $Z=O$ , or where  $X=OR$ ,  $Y=NH$  or  $NR'$ , and  $Z=O$ , and  $R$  and  $R'$  are groups which do not interfere with target binding.

4. The compound of claim 3, wherein  $R$  and  $R'$  are moieties independently selected from alkyl, polyalkyleneoxy, and a combination thereof, which may be substituted with one or more groups selected from hydroxy, alkoxy, amino, alkylamino, thiol, alkanethiol, halogen, oxo, carboxylic acid, carboxylic ester, and inorganic ester.

5. The compound of claim 4, wherein each said moiety  $R$  and  $R'$ , independent of substitution, is from 1 to 6 atoms long.

6. The compound of claim 3, wherein  $NRR'$  represents a nitrogen heterocycle having 5-7 ring atoms selected from nitrogen, carbon, oxygen, and sulfur, and having at least as many carbon ring atoms as non-carbon ring atoms.

7. The compound of claim 6, wherein the 5' end of the target region is 10-15 bases downstream of a normal splice acceptor site.

8. The compound of claim 1, wherein the selected protein is human *c-myc*.

9. The compound of claim 8, wherein the base sequence is selected from the group consisting of SEQ ID NOs: 16 through 32.

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10. The compound of claim 9, wherein the base sequence is SEQ ID NO: 25.
11. The compound of claim 8, wherein the base sequence is a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 34.
12. The compound of claim 11, wherein the base sequence is SEQ ID NO: 33.
13. The compound of claim 1, wherein the selected protein is human androgen receptor, and the base sequence is a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 9 or SEQ ID NO: 13.
14. The compound of claim 13, wherein the base sequence is SEQ ID NO: 8 or SEQ ID NO: 12.
15. The compound of claim 1, wherein the selected protein is HCG- $\beta$  subunit, and the base sequence is a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 15.
16. The compound of claim 15, wherein the base sequence is SEQ ID NO: 14.
17. The compound of claim 1, wherein the selected protein is human p53, and the base sequence is a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 36.
18. The compound of claim 17, wherein the base sequence is SEQ ID NO: 35.
19. The compound of claim 1, wherein the selected protein is human abl, and the base sequence is a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 38.
20. The compound of claim 19, wherein the base sequence is SEQ ID NO: 37.
21. The compound of claim 1, wherein the selected protein is HIV-1 rev, and the base sequence is a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 41.
22. The compound of claim 21, wherein the base sequence is SEQ ID NO: 40.
23. A method of inhibiting normal splicing of mRNA in a eukaryotic cell, comprising contacting the cell with an antisense compound having an uncharged morpholino backbone and a base sequence between 12 and 25 nucleotide bases in length which is

complementary to a target region of a selected preprocessed mRNA coding for a selected protein; where the 5' end of the target region is 1-25 bases downstream of the a normal splice acceptor site in said preprocessed mRNA,

wherein the compound:

- 5 is taken up by the cell;  
hybridizes to the target region of preprocessed mRNA in the cell, and  
being so hybridized, prevents splicing at said normal acceptor splice site, such that the splice mechanism proceeds to a downstream splice acceptor sequence in the mRNA, producing a splice variant processed mRNA with a truncated coding sequence.

24. The method of claim 23, wherein the protein is selected from the group consisting of *myc*, *myb*, *rel*, *fos*, *jun*, *abl*, *bcl*, *p53*, an integrin, a cathedrin, a telomerase, hCG, a receptor protein, a cytokine, a kinase, HIV rev, human papilloma virus, and human parvovirus B19.

25. The method of claim 24, wherein the compound has intersubunit linkages selected from the group consisting of the structures presented in Figs. 2AA-2EE.

26. The method of claim 25, wherein the linkage is the phosphorodiamidate linkage represented at Figure 2B-B, where  $X=NH_2$ ,  $NHR'$ , or  $NRR'$ ,  $Y=O$ , and  $Z=O$ , or where  $X=OR$ ,  $Y=NH$  or  $NR'$ , and  $Z=O$ , and  $R$  and  $R'$  are groups which do not interfere with target binding.

27. The method of claim 26, wherein  $R$  and  $R'$  are moieties independently selected from alkyl, polyalkyleneoxy, and a combination thereof, which may be substituted with one or more groups selected from hydroxy, alkoxy, amino, alkylamino, thiol, alkanethiol, halogen, oxo, carboxylic acid, carboxylic ester, and inorganic ester.

28. The method of claim 27, wherein each said moiety  $R$  and  $R'$ , independent of substitution, is from 1 to 12 atoms long.

29. The method of claim 26, wherein  $NRR'$  represents a nitrogen heterocycle having 5-7 ring atoms selected from nitrogen, carbon, oxygen, and sulfur, and having at least as many carbon ring atoms as non-carbon ring atoms.

30. The method of claim 23, wherein the 5' end of the target region is 10-15 bases downstream of a normal splice acceptor site.

31. The method of claim 23, wherein said downstream splice acceptor site is a whole multiple of three bases downstream of the normal splice acceptor site, such that said splice variant mRNA has a coding sequence in frame with that of the processed mRNA when it is normally spliced.

32. The method of claim 23, wherein the selected protein has multiple distinct binding regions, and said truncated coding sequence codes for a variant protein in which a binding region is disabled.

33. The method of claim 32, wherein said variant protein is a dominant negative protein.

34. The method of claim 33, wherein said selected protein is human *c-myc*, and said variant protein is an N-terminal truncated *c-myc* protein.

35. The method of claim 34, wherein the antisense compound has a base sequence selected from the group consisting of SEQ ID NOs: 16 through 32.

36. The method of claim 35, wherein the antisense compound has the base sequence SEQ ID NO: 25.

37. The method of claim 23, wherein the selected protein and corresponding antisense base sequence are selected from the group consisting of:

(a) human chorionic gonadotropin,  $\beta$  subunit: a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 15;

(b) human androgen receptor: a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 9 or SEQ ID NO: 13;

(c) human *c-myc*: a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 34;

(d) human p53: a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 36;

(e) human *abl*: a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 38; and

(f) HIV-1 rev: a contiguous 18- to 20-nucleotide sequence selected from SEQ ID NO: 41.

38. The method of claim 37, wherein the selected protein and corresponding antisense base sequence are selected from the group consisting of:

- (a) human chorionic gonadotropin,  $\beta$  subunit: SEQ ID NO: 14;
- (b) human androgen receptor: SEQ ID NO: 8 or SEQ ID NO: 12;
- (c) human *c-myc*: SEQ ID NO: 33;
- (d) human p53: SEQ ID NO: 35;
- (e) human abl: SEQ ID NO: 37; and
- (f) HIV-1 rev: SEQ ID NO: 40.

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